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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/218,660	12/22/1998	EVAN C. UNGER	UNGR-1520	2775

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EXAMINER

SHARAREH, SHAHNAM J

ART UNIT PAPER NUMBER

1617

DATE MAILED: 12/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/218,660

Applicant(s)

UNGER ET AL.

Examiner

Shahnam Sharareh

Art Unit

1617

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 28 September 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) See Continuation Sheet is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) See Continuation Sheet is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

Continuation of Disposition of Claims: Claims pending in the application are 100,102,127,194-200,203,210-213,217-228,294-300,303,310-329,331-337,347-356 and 412.

Continuation of Disposition of Claims: Claims rejected are 100,102,127,194-200,203,210-213,217-228,294-300,303,310-329,331-337,347-356 and 412.

DETAILED ACTION

1. Amendment filed on September 28, 2005 has been entered. Claims 100, 102, 127, 194-200, 203, 210-213, 217-228, 294-300, 303, 310-329, 331-337, 347-356, 412 are pending.

Priority

2. The effective priority date used for the examination of the instant application is May 1, 1996. Applicant arguments about the priority date have been fully considered but are not found persuasive. Applicant is informed that in order to receive the benefit of an earlier filing Applicant must first convey the inventive concept of the claim as a whole consistent with the requirements of the USC § 112 first paragraph. For example, if Applicant conveyed the concept of using phospholipid mixture as the shell material in one chain of applications and conveyed the concept of using a fluorinated gas in another chain of applications but did not convey the concept of combining the two together until the instant application, then the effective priority date of that claim would be that of the instant application. Accordingly, the effective priority date of the instant application is May 1, 1996, because the invention as a whole was first disclosed at this date.

3. Applicant argues that the claims as amended have an effective filing date of June 7, 1995, the filing date of US Application SN 08/497,684 (US '684). Applicant adds that the instant case is a continuation in part of the case US '684 and all the intervening child applications were copending before the filing of the instant case. (see Remarks at page 14-15).

Art Unit: 1617

4. Applicant is first informed that the requirement under 35 USC §112, first paragraph, for "written description of the invention" is separate and distinct from the requirement for enablement. The purpose of the "written description" requirement is broader than to merely explain how to "make and use" or simply disclose an element of a claimed invention; rather, the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. MPEP 2163.05 (I). Although one might not have to describe exactly the subject matter claimed, the description must clearly allow persons of ordinary skill in the art to recognize that the inventor invented what is claimed. In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989), MPEP 2163.02.

5. Accordingly, the test for sufficiency of support in a parent application is whether the disclosure of the application relied upon, "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." Ralston Purina Co. v. Far-Mar-Co, Inc., 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (quoting In re Kaslow, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983)). Therefore in the instant case, the possession of the invention as a whole is assessed based on the combined features of the claimed formulation such as the claimed gas species in combination with the specific phospholipids, gas mixtures; linking groups of polymeric moiety covalently bound to the phospholipids and the targeting ligand, of proteins, peptides, steroids and genetic material or any specific ligands enumerated in the dependent claims. For the broad use of therapeutic

Art Unit: 1617

methods, each elemental step needs to have been adequately described in the parent application. Such teachings lack in the parent cases.

6. Here, applicant referring to specific portions of the patent application, states that the instant limitations are generically described in the parent application (see Remarks at page 15). In response, Examiner states that "the question under a [Written Description Rejection] is not whether a claimed invention is an obvious variant of that which is disclosed in the specification. Rather, the application itself must describe an invention, and do so in sufficient detail that one skilled in the art can clearly conclude that the inventor invented the claimed invention as of the filing date sought. See Lockwood v. American Airlines Inc., 107 F3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed Cir. 1997) citing Martin v. Mayer, 823 F.2d 500, 504, 3 U.S.P.Q.2D (BNA) 1333, 1337 (Fed. Cir. 1987). In fact, one must show that one is "in possession" of the invention by describing the invention, with all its claimed limitations, not that which makes it obvious. Id.

7. Examiner adds that nowhere in the parent cases has the applicant exemplified or provided any evidence that the current pending claims were indeed in possession. There is no composition comprise all components of the instant claims. For example, Examiner can not find a formulation that comprise gaseous vesicles comprising a phospholipids membrane containing perfluorohexane, a hydrophilic polymer that is of polypropylene glycol that is covalently attached to such phospholipids and then is further bounded to a targeting agent comprising the sequence Lys-Gln-Ala-Gly-Asp-Val.

8. Applicant has a burden of clearly conveying the invention that he has in possession. Applicant has not done so. Thus, the priority of the instant application is May 1996 because the possession of the instant claimed invention as a whole is assessed based on the combined features of the product and the process steps.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

9. Claims 100, 102, 127, 194-200, 203, 210-213, 217-220, 294-300, 303, 310-317, 326, 412 are rejected under 35 U.S.C. 103(a) as being unpatentable over Allen US Patent 5,620,689 (Allen) in view of Wallach US Patent 4,853,228 (Wallach), Schneider US Patent 5,643,553 (Schneider) and Porter US Patent 5,648,098 (Porter).

10. Applicant's arguments with respect to this rejection have been fully considered but are not found persuasive.

11. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Here, the combined teachings of the cited references meet the limitations of the instant claims. Therefore, the rejection is proper.

12. First, Applicant argues that none of the cited references teach gas-filled vesicles wherein the gas is a perfluorocarbon or sulfur hexafluoride (see Remarks at page 16, last para.). In reply, Examiner states that clearly Schneider and Porter meet such

limitations. Schneider for example teaches liposomal composition comprising gas-filled microbubbles, wherein the microbubbles may contain various surfactant such as a microbubble shell forming phospholipid or more specifically PE, as well as, polymeric surfactants, such as PEG surfactants, (col 6, lines 25-64; claims 4-20). Schneider also teaches that targeting ligands (e.g, polypeptides, antibodies, etc..) may be bounded by the stabilizing surfactant layer of the microbubbles to provide site-specific targeting of the diagnostic or therapeutic microbubbles (see col 9, lines 10 +, example 11).

13. Schneider further teaches specific types of gases that are suitable to be entrapped inside the vesicles. (see col 9, lines 39-45). Such gases include freons, which generically represent small molecule perfluorocarbon gases such as C₂F₆ or CF₄ etc.. Thus, Schneider teaches microbubbles that comprise PE shells combined with a PEG surfactant, which may be bound with a peptide targeting ligand and can contain Freons that encompass perfluorocarbon gases.

14. In the last Office Action Examiner acquiesced to the fact that Schneider does not explicitly teach a perfluorinated gaseous liposome that is covalently bound to a targeting ligand via a PEG linker. (see Office Action at page 3). Examiner merely made such statement to inform Applicant that Schneider only fails to exemplify such type liposomes. Nevertheless, Schneider provides ample motivation in the art and reasonable expectation of success for preparing a perfluorinated gaseous liposome that is covalently bound to a targeting ligand via a PEG linker.

15. Moreover, Porter's teachings complement those of Schneider. Porter teaches method of improving drug activity when microvesicles contains perfluorocarbon gas,

which cavitate in the presence of an ultrasound field. (see abstract; col 8, lines 19-45).

Porter not only exemplify perfluorobutane as a suitable gas to be entrapped in a microbubble, but also as the type of gas that can improve the clinical outcome (see col 8, lines 38-42).

16. Second, in response to Applicant's arguments that Allen does not teach gas-containing vesicles, Examiner states that, had Allen provided such specific teachings, it would have been used as an anticipatory reference under 35 USC 102. However, here the rejection uses Allen as the primary reference in an obviousness analysis.

Allen is used to show that targeted lipid vesicles are used for delivery of diagnostic or therapeutic agents. Allen teaches vesicle shell attached to a polymer chain of PEG having a molecular weight of between 500-10000 dalton which is attached covalently to an antibody (see col 2, lines 55-66; col 5-6; fig. 1, col 11, lines 38-66; col 12, lines 29-34). Allen's liposomes contain entrapped therapeutic agents and imaging agents (see col 7, lines 30-55).

17. As described by Schneider and Porter, gases such as Freons and perfluorocarbons are viewed as imaging agents. Thus, one of ordinary skill in the art at the time of invention in possession of such teachings would have had a reasonable expectation of success in using an imaging agent such as the gases of Schneider and Porter in vesicles of Allen.

18. Wallach's teachings are complementary to Allen's as it explicitly describes the covalent bonding between the linker, targeting agent and the phospholipids moiety of a liposomal shell. (see col 5, lines 8-30; col 10, lines 10-42; col 4, lines 61+; col 9, lines

Art Unit: 1617

10-36). Wallach specifically teaches that the targeting ligand may be conjugated to the microspheres by covalent attachment of the targeting molecule to the amino group of PE via a spacer group of polyoxyethylene head groups, (see col 5, lines 1-7). The vesicles of Wallach do not contain a disulfide linkage.

19. Thus, it would have been obvious to one of ordinary skill in the art at the time of invention to further incorporate a gaseous ultrasound contrast agent of Schneider in the liposomes of Allen and Wallach and use such formulations for therapeutic or diagnostic purposes, because as suggested by both Allen and Wallach, the liposomes can contain a contrast agent.

20. Finally, Applicant argues that Porter is not a compentant prior art because it has an effective filing date that is after the instant application. However, for the reasons set forth above the priority of the instant case is May 1, 1996. For such reasons and those of record, Examiner maintains the rejection

21. Claims 318-325, 327-329, 331-337, 347-356 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Allen in view of Wallech, Schneider and Porter as applied to claims 100, 102, 127, 194-200, 203, 210-213, 217-220, 294-300, 303, 310-317, 326, 412 and further in view of Ginsburg US Patent 5,656,442 (Ginsburg).

22. Applicant has not offered any additional argumenents with respect to this rejection. Accordingly, it is maintained for the reasons of record.

Conclusion

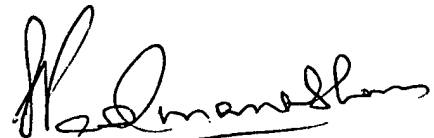
23. No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shahnam Sharareh whose telephone number is 571-272-0630. The examiner can normally be reached on 8:30 am - 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, PhD can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.


SREENIVASAN PADMANABHAN
SUPERVISORY PATENT EXAMINER

Art Unit: 1617

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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